PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference CAM10 (WO)	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/GB2005/000464	International filing date *(day/month/year)* 11 February 2005 (11.02.2005)	Priority date *(day/month/year)* 11 February 2004 (11.02.2004)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant CAMBRIDGE LABORATORIES (IRELAND) LIMITED		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 14 August 2006 (14.08.2006)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Nora Lindner e-mail: pt02@wipo.int

Form PCT/IB/373 (January 2004)

25/08

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2005/000464	11.02.2005	11.02.2004

International Patent Classification (IPC) or both national classification and IPC
C07D455/06, A61K31/473, A61P25/14

Applicant
CAMBRIDGE LABORATORIES LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 27 (with regard to industrial applicability)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 27 (with regard to industrial applicability)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-34
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-34
Industrial applicability (IA)	Yes:	Claims	1-26, 28-34
	No:	Claims	-

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 27 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.1 Cited documents

D1: M. R. KILBOURN ET AL: "Absolute Configuration of (+)-alpha-Dihydrotetrabenazine, an Active Metabolite of Tetrabenazine" CHIRALITY, vol. 9, no. 1, 1997, pages 59-62, XP002329921

D2: M. KILBOURN ET AL: "Binding of alpha-dihydrotetrabenazine to the vesicular monoamine transporter is stereospecific" EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 278, no. 3, 1995, pages 249-252, XP002329922

D3: A. BROSSI ET AL: "Syntheseversuche in der Emetin-Reihe. 3. 2-Hydroxy-hydrobenzo[a]chinolizine" HELVETICA CHIMICA ACTA, vol. 41, 1958, pages 1793-1806, XP008047475 BASEL, CH

D4: US-A-6 087 376 (CROOKS ET AL) 11 July 2000 (2000-07-11)

D5: US-A-2 843 591 (A. BROSSI ET AL) 15 July 1958 (1958-07-15)

D6: US-A-2 830 993 (A. BROSSI ET AL) 15 April 1958 (1958-04-15)

The indicated designations are used throughout the examination procedure.

V.2 Novelty

None of the cited documents disclose a dihydrotetrabenazine isomer where the hydrogen atoms at positions 3 and 11b are in "cis"-position. Moreover, none of the cited documents disclose compounds as claimed in claims 32, 33 and 34.

Therefore the subject-matter of the compound claims (1-23, 32-34), the pharmaceutical claims (24-27) and the process claims (28-31) is considered novel.

V.3 Inventive step

V.3.1 According to the description, the problem underlying the present application is to provide further dihydrotetrabenazine derivatives which are therapeutically useful.

V.3.2 Some of the possible stereoisomers of dihydrotetrabenazine are already known from the art, (see D1, D2 and D3, which are considered as relevant prior art). The applicant has now provided stereoisomers of tetrahydrobenazine which have a "cis"-configuration with regard to the positions 3 and 11b. All of the tetrahydrobenazine isomers hitherto known appear to have the "trans"-configuration with regard to the positions 3 and 11b.

V.3.3 Tetrabenazine and dihydrotetrabenazine are known in the art to inhibit the vesicular monoamine transporter (VMAT2) in the brain and also the dopamine receptors. The applicant points out that the dihydrotetrabenazine isomers according to the application are also inhibitors of VMAT2. This result is not unexpected in view of the close chemical similarity of the present compounds and the known dihydrotetrabenazines.

V.3.4 The person skilled in the art, having in mind the stereochemical configuration of the dehydrobenazines hitherto known in the art ("trans" isomers) is well aware of the remaining isomers which have not been prepared yet ("cis" isomers). The skilled person would have the expectation that the pharmacological activity profile of the "cis" isomers is similar to the known ones. This seems to be actually the case.

V.3.5 The description contains biological test results for all of the four possible (and claimed) isomers, which show that there are significant activity differences among these isomers. However, the applicant does not seem to have carried out a comparison between the claimed compounds and the compounds known from the art. So it can only be said that the present compounds have pharmacological effects similar to the tetrahydrobenazines disclosed in the prior art.

V.3.6 Since those effects as such were (qualitatively) to be expected by a skilled person, the presence of an inventive step cannot be acknowledged for the subject-matter of the compound claims 1-23 and for the pharmaceutical claims 24-27.

V.3.7 Inventive step is also to be denied for the subject-matter of the process claims 28-31 and for claims 32-34, which are directed to intermediates. This is because the subject-matter of claims for processes and intermediates can only be considered inventive if the intermediates are precursors in processes which lead to inventive end products.

V.3.8 Inventive step, however, could have been acknowledged if the applicant had been able to make credible that with the presently claimed compounds a technical problem was solved or a technical effect was obtained which can be considered non-obvious with regard to the prior art disclosures.

V.4 Industrial applicability

V.4.1 The subject-matter of claims 1-26 and 28 -34 is industrially applicable.

V.4.2 For the assessment of the present claim 27 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VII

Certain defects in the international application

Claims 15 to 20 do not comply with Rule 6.2(a) PCT since they rely, in repect of the technical features of the invention, on references to the description (i.e. the tables).

Re Item VIII

Certain observations on the international application

In claim 2, the term "for example" makes the claim unclear as to the very subject-matter for which protection is sought (Art. 6 PCT). Moreover, the claims contain three different embodiments (ranges) concerning the isomeric purity which also make the claim unclear ("greater than..., *typically* greater than..., *more preferably* greater than..."). Therefore the three embodiments should have been split off into three claims. This objection applies to claim 5 accordingly: Claim 5 also contains three different ranges of by-products which make the claim unclear as to the very scope for which protection is sought ("less than..., *preferably* less than..., *more preferably* less than..."). Therefore also claim 5 should have been divided into three claims.